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Abstract: *Background:* Heart failure (HF) with preserved ejection fraction (pEF) has lacked effective treatments for reducing mortality. However, previous studies have found an association between statin use and decreased mortality in patients with HFpEF. The aim of this study was to analyze whether statin therapy is associated with a reduction in mortality in these patients and whether the effect differs according to presence or absence of ischemic heart disease (IHD). *Methods:* We analyzed data from the National Registry of Heart Failure, a prospective study including patients admitted for HF in Internal Medicine units nationwide. Patients with HFpEF were classified according to the use of statins and differences between two groups were analyzed. A multivariate analysis was performed using Cox regression to assess factors independently related to mortality. *Results:* 2788 patients with HFpEF were included, 63% of them were women with a mean age of 80.1(±7.8) years. The statin-treated group (40.2%) was younger, with better functional status, and had a more common diagnosis of vascular disease and lower frequency of atrial fibrillation. The most frequent etiology of HF in both groups was the hypertensive one. Nevertheless, ischemic HF was more common in those who received statins (24.8% vs. 9.6%; p<0.001). Multivariate analysis showed lower mortality at 1-year follow-up in statin-treated patients (OR:0.74; 95%CI:0.61-0.89; p=0.002). This association was observed in patients without IHD (p<0.001), but not in those with IHD (p=0.11). *Conclusion:* Statins are associated with a decrease in total mortality in patients with HFpEF. This benefit occurs mainly in those without IHD.

Keywords: heart failure; preserved ejection fraction; mortality; statins

1. Introduction

Heart failure (HF) is a leading cause of hospitalization and death in people over 65 years of age, and predominantly affects older patients [1,2]. This syndrome is classified according to left

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ventricular ejection fraction (EF) in HF with preserved EF (HFpEF) (≥50%), HF with reduced EF (HFrEF) (≤40%), and HF with mildly reduced ejection fraction (HFmrEF) (41-49%). HFpEF accounts for approximately half of all HF patient and its prevalence is increasing [1]. Until recently, in this type of HF, in contrast to HFrEF, no drug has been shown to reduce mortality [1–3]. In fact, only sodium-glucose cotransporter type 2 inhibitors (iSGLT2), have recently shown to reduce the combined risk of readmissions and cardiovascular mortality of patients with HFpEF [4,5], and some meta-analyses showed a decrease in isolated cardiovascular mortality, not in individual clinical trials [6,7]. Nevertheless, the effect of beta-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (ARBs), angiotensin receptor neprilysin inhibitors (ARNi), digoxin and ivabradine, have been analyzed without benefit [8].

Several observational studies have shown reduction in mortality with the use of statins in patients with HFpEF [9–24]. Some of them suggest that this effect is independent of LDL cholesterol level [9,15,24,25]. Benefit has even been found in patients with HFpEF of non-ischemic etiology [12,15,25]. It is also worth mentioning that several meta-analysis supports a decrease in mortality in patients with HFpEF taking statins [9,20,26,27]. Nevertheless, the efficacy of statins in patients with HFrEF outside the indication of coronary heart disease has not been demonstrated, as was found in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) clinical trial, in which rosuvastatin did not reduce mortality, but did reduce hospitalizations due to cardiovascular causes [28]. Similarly, another clinical trial, (GISSI trial), showed no decrease in mortality in patients treated with statins (Rosuvastatin). This was the only clinical trial conducted that analyzed patients with HFrEF and HFpEF separately. However, only 10% of patients had HFpEF [29].

The lack of effective therapies in HFpEF, and insufficient evidence on the benefit of statins without clinical trials in this type of HF [3], make it necessary to study the impact of these drugs, and especially if they have a role in patients without ischemic heart disease as some studies have suggested [15,25]. Statins may represent a change in the current management of these patients. Despite this, the latest HF guidelines state that statins are only indicated for coronary artery disease [3,30], probably due to limited evidence and some studies denying their benefit, unless otherwise specifically indicated [21,29].

The purpose of this study is to analyze whether statin therapy improves the prognosis of patients with HFpEF and especially whether the effect differs according to the presence or absence of ischemic heart disease.

2. Materials and Methods

2.1. Design

An observational study was conducted using data from the National Registry of Heart Failure (RICA). The RICA registry is a prospective multicenter cohort study with the aim of analyzing the characteristics of patients admitted for HF in Internal Medicine units nationwide.

2.2. Population, Study Scope and Recruitment

This registry includes data from patients from 52 Spanish hospitals. These patients were over 50 years of age discharged after a hospitalization due to HF (either debut or exacerbated chronic) and followed up for at least one year. All patients had to have echocardiography to assess LVEF and the diagnosis of HF was made according to the criteria of European Society of Cardiology [4].

For this study, only patients with a diagnosis of HFpEF were included, from March 2008 to September 2018. Patients with HF secondary to severe pulmonary hypertension, refusal to participate, patients currently participating in a clinical trial or those who could not be followed up were excluded. The follow-up consists in a three month and one year visit. The readmissions and mortality was collected.

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2.3. Study Variables

Socio-demographic characteristics (age, sex), height, weight, body mass index (BMI), functional capacity (assessed by the Barthel index [31]) and mental status by the Pfeiffer test [32] were collected.

Comorbidities were also included using the Charlson Index [33], as well as other comorbidities not included in this index such as arterial hypertension, dyslipidemia, atrial fibrillation and anemia.

Functional class according to the New York Heart Association (NYHA) classification and heart rate (HR) and some vital signs like systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also recorded.

Some blood tests data such as creatinine, hemoglobin, estimated glomerular filtration rate (eGFR) and N-terminal portion of B-type natriuretic peptide (NT-proBNP) were recorded. It was also included the treatment prescribed at discharge: statins, beta-blockers, ACE inhibitors, ARA II, aldosterone antagonists, loop diuretics, thiazide diuretics, digoxin and ivabradine.

2.4. Statistical Analysis

Initially, a descriptive study was carried out. Categorical variables were expressed as frequencies and percentages and quantitative variables as mean and standard deviation (SD) or as median and interquartile range, depending on whether the distribution was normal or non-normal.

Subsequently, differences between patients according to whether they received statin treatment or not were analyzed. The Chi-square test or Fisher's exact test was used to assess the relationship between categorical variables and the Student's t-test or Mann-Whitney U test for quantitative variables, depending on whether the variables followed a normal distribution or not. The by Kolmogorov-Smirnov test was used to determine whether quantitative variables were normally distributed. All-cause mortality after 1 year was analyzed in both groups, treated or not with statins and Kaplan-Meier curves were built to observe the prognostic differences between both groups. To assess whether statin use was independently associated with mortality, a multivariate analysis was performed using Cox regression model, including variables that in the univariate analysis, showed a statistically significant relation with the probability of death.

To assess whether the effect of statins differed in patients with and without ischemic heart disease, mortality-related factors were analyzed separately in both groups by univariate and multivariate Cox regression analysis. A p-value of less than 0.05 was considered statistically significant. The odds ratio (OR) and hazard ratio (HR) were used as a measure of the magnitude of association and were expressed together with their 95% confidence interval (95% CI). Statistical analysis was performed with SPSS software (Statistical Package for the Social Sciences, IBM Corp. IBM SPSS Statistics for Windows, Version 29.0, Armonk, New York: IBM Corp).

2.5. Ethical Considerations

The RICA registry protocol conforms to the ethical guidelines of the Declaration of Helsinki and it was approved by the Ethics Committee of the Hospital Universitario Reina Sofía (Córdoba) and all patients signed the informed consent before being included in the RICA cohort. The registry protocol was initially approved by the Ethics Committee of the Hospital Universitario Reina Sofía de Córdoba and was subsequently approved by each of the committees of the participating hospitals (code 18/349-E, last updated on 9 August 2018). All patients signed an informed consent form prior to inclusion in the registry. The data were collected from a web page (www.registrorica.org, accessed on 1 January 2008) containing the anonymous database and accessed by each investigator through a personalized password.

3. Results

3.1. Descriptive Analysis

A total of 2788 patients with a diagnosis of HFpEF were included, of whom 1031 (37%) were male and 1757 (63%) female, with a mean age of 80.1 years ± SD: 7.8; range 50-100 years.

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3.2. Characteristics of Patients on Statin Therapy

Of the total, 1121 (40.2%) patients were taking statins and 1667 (59.8%) were not. The relationship between statin intake and demographic characteristics and comorbidities is detailed in Table 1.

Table 1. Demographic characteristics, comorbidities and scales of assessment of patients with HFpEF according to whether they were taking statins or not.

	Total N=2788	**Statin-treated N=1121 (40.2%)**	**Not treated N= 1667 (59.8%)**	***p***	**OR (95% CI)**
Demographics					
Age (years).*	80.1 ± 7.8	79.4 ± 7.6	80.5 ± 8	**<0.001**	0.98 (0.97-0.99)
Sex: Women,**	1757 (63)	703 (62.7)	1054 (63.2)	0.782	0.97 (0.84-1.14)
Men,**	1031 (37)	418 (37.3)	613 (36.8)		
Comorbidities					
Hypertension,**	2470 (88.6)	1040 (92.8)	1430 (85.8)	**<0.001**	2.13 (1.63-2.77)
Diabetes,**	1255 (45)	631 (56.3)	624 (37.4)	**<0.001**	0.47 (0.40-0.54)
Dyslipidemia,**	1368 (49,1)	921 (82.2)	447 (26.8)	**<0.001**	0.08 (0.07-0.09)
Obesity (IMC > 30),**	1204 (43.2)	520 (46.4)	684 (41)	**0.005**	1.24 (1.07-1.45)
Myocardial infarction, **	465 (16.7)	308 (27.5)	157 (9.4)	**<0.001**	0.27 (0.22-0.34)
Stroke, **	370 (13.3)	189 (16.9)	181 (10.9)	**<0.001**	0.60 (0.48-0.75)
Peripheral arterial disease, **	250 (9)	127 (11.3)	123 (7.3)	**<0.001**	0.62 (0.48-0.81)
Atrial fibrillation (ECG), **	1699 (60.9)	626 (55.8)	1073 (64.6)	**<0.001**	0.70 (0.60-0.82)
COPD, **	651 (23.4)	236 (21.1)	415 (24.9)	**0.019**	1.24 (1.04-1.49)
Dementia, **	141 (5.1)	42 (3.7)	99 (5.9)	**0.010**	1.62 (1.12-2.35)
Neoplasia, **	311 (11.2)	115 (10.3)	196 (11.8)	0.218	1.17 (0.91-1.49)
Anemia, **	1613 (57.9)	667 (59.5)	946 (56.7)	0.149	1.12 (0.96-1.31)
eGFR < 60 ml/min, **	1624 (58.2)	678 (60.5)	946 (56.7)	0.050	1.17 (1-1.36)
Hiponatremia, **	424 (15.2)	171 (15.3)	253 (15.2)	0.956	1 (0.81-1.24)
Scales of assessment					
Charlson Index, *	2.8 ± 2.4	3.2 ± 2.4	2.55 ± 2.3	**<0.001**	1.12 (1.08-1.16)
Barthel Index, *	80.6 ± 23	82.4 ± 21.9	79.4 ± 23.7	**<0.001**	1.006 (1.002-1.009)
Barthel Index < 60, **	470 (16.9)	161 (14.4)	309 (18.5)	**0.004**	0.74 (0.60-0.91)
Pfeiffer Test, *	1.63 ± 2	1.5 ± 1.8	1.7 ± 2.1	**0.003**	0.94 (0.91-0.98)
Pfeiffer Test ≥ 3 wrong, **	628 (25.4)	237 (22.8)	391 (27.2)	**0.012**	0.79 (0.65-0.95)

Legend: Categorical variables are expressed in number and percentage: **n (%). Quantitative variables are expressed as *mean ± standard deviation (SD). OR: odds ratio; 95% CI: 95% confidence interval; BMI: body mass index; ECG: electrocardiogram; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate.

Patients receiving statin treatment at discharge were younger (mean 79.4 vs. 80.5 years; p<0.001), with no significant differences in sex compared to those who did not take statins.

Regarding medical history, statin-treated patients were significantly more likely to have hypertension, diabetes, dyslipidemia and obesity. In addition, they had more history of myocardial infarction, ischemic stroke, and peripheral arterial disease. Conversely, they had less atrial fibrillation, dementia, and chronic obstructive pulmonary disease (COPD). Patients on statin therapy had higher comorbidity as assessed by the Charlson index (mean 3.2 vs. 2.55; p<0.001).

On the other hand, patients on statin treatment had a better functional and mental status with lower functional dependency according to the Barthel index and a Pfeiffer test with fewer errors (Table 1).

Regarding the etiology of HF (Table 2), hypertension was the most frequent cause of HF in both groups, although it predominated, almost significantly, in patients without statins (51.5% vs. 47.7%;

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p=0.053). Ischemic etiology was higher in statin-treated patients (24.8% vs. 9.6%; p<0.001), while valvular etiology was less frequent in this group (16.6% vs. 22.7%; p<0.001).

Statin-treated patients had a better NYHA functional class. There was no difference in the percentage of debut HF between the two groups.

Regarding pharmacological treatment at discharge (Table 2), statin-treated patients received more ACE inhibitors or ARBs, beta-blockers, loop diuretics and ivabradine, while more non-treated patients were treated with digoxin.

At 1-year follow-up, patients receiving statins had more readmissions for any cause (41.8% vs. 37.8%; p=0.030) and for HF (25.5% vs. 21%; p=0.005). However, 1-year all-cause mortality was significantly lower in this group of patients (14.7% vs. 20.9%; p<0.001).

Table 2. Characteristics of heart disease, vital signs, blood test data, treatment at discharge and outcome (deaths and readmissions at one year) of patients with HFpEF according to the intake of statins.

	Total N=2788	**Statin-treated N = 1121 (47.2%)**	**Not treated N = 1667 (59.8%)**	***p***	**OR (95% CI)**
LVEF (%), *	61.8 ± 8.1	61.3	62.1	**0.014**	0,988 (0,98-0,99)
NYHA: I-II, ** III-IV, **	1782 (65.1) 954 (34.9)	750 (67.4) 363 (32.6)	1032 (63.6) 591 (36.4)	**0.040**	0,85 (0,72-0,99)
debut HF, **	928 (33.3)	367 (32.7)	561 (33.7)	0.615	0,96 (0,82-1,13)
Etiology of HF					
Hypertensive **	1393 (50)	535 (47.7)	858 (51.5)	0.053	0.86 (0.74-1)
Ischemic, **	438 (15.7)	278 (24.8)	160 (9.6)	**<0.001**	3.12 (2.51-3.84)
Valvular, **	565 (20.3)	186 (16.6)	379 (22.7)	**<0.001**	0.68 (0.56-0.82)
Hypertrophic, **	51 (1.8)	18 (1.6)	33 (2)	0.470	0.81 (0.45-1.44)
Alcoholic, **	10 (0.4)	3 (0.3)	7 (0.4)	0.510	0.64 (0.16-2.47)
Non-affiliated, **	164 (5.9)	50 (4.5)	114 (6.8)	**0.009**	0.64 (0.45-0.90)
Others, **	147 (5.3)	39 (3.5)	108 (6.5)	**0.001**	0.52 (0.36-0.76)
Vital signs					
SBP (mmHg), *	140.3 ± 27.1	142.2 ± 27.4	139 ± 26.8	**0.002**	1.004 (1.002-1.007)
DBP (mmHg), *	75 ± 15.9	74.8 ± 15.6	75.1 ± 16	0.590	0.99 (0.992-0.996)
HR (lpm), *	86.1 ± 22.3	84.8 ± 21.4	86.9 ± 22.8	**0.015**	0.999 (0.994-1.003)
Blood test data					
Cr (mg/dl), *	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7	0.065	1.11 (0.99-1.24)
Hb (g/dl), *	11.9 ± 2	11.8 ± 2	11.9 ± 2	0.271	0.98 (0.94-1.02)
NT-proBNP (pg/ml), *	5190.6 ± 6174.9	5102.2 ± 5870.1	5253.9 ± 6387.9	0.666	1.01 (0.99-1.03)
Discharge treatment					
ACE inh., **	994 (35.7)	413 (36.8)	581 (34.9)	0.282	1.09 (0.93-1.28)
ARBs, **	838 (30.1)	401 (35.8)	437 (26.2)	**<0.001**	1.57 (1.33-1.85)
ACE inh. or ARBs, **	1809 (64.9)	804 (71.7)	1005 (60.3)	**<0.001**	1.67 (1.42-1.97)
Beta-blockers, **	1437 (51.5)	671 (59.9)	766 (46)	**<0.001**	1.75 (1.50-2.05)
Loop diuretics, **	2383 (85.5)	1012 (90.3)	1371 (82.2)	**<0.001**	2.00 (1.59-2.53)
Aldosterone antagonists, **	621 (22.3)	254 (22.7)	367 (22)	0.689	1.04 (0.86-1.24)
Thiazide diuretics, **	290 (10.4)	123 (11)	167 (10)	0.418	0.90 (0.71-1.16)
Ivabradine, **	28 (1)	20 (1.8)	8 (0.5)	**0.001**	3.77 (1.65-8.58)
Digoxin, **	550 (19.7)	180 (16.1)	370 (22.2)	**<0.001**	0.67 (0.55-0.82)
Deaths and readmissions after 1 year					
Deaths, **	514 (18.4)	165 (14.7)	349 (20.9)	**<0.001**	0.65 (0.53-0.80)
Readmissions, **	1098 (39.4)	468 (41.8)	630 (37.8)	**0.033**	0.85 (0.72-0.99)
Readmissions for HF, **	636 (22.8)	286 (25.5)	350 (21)	**0.005**	0.78 (0.65-0.93)

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Legend: Categorical variables are expressed in number and percentage: **n (%). Quantitative variables are expressed as *mean ± standard deviation (SD). OR: odds ratio; 95% CI: 95% confidence interval; LVEF: left ventricle ejection fraction; NYHA: Functional Classification of the New York Heart Association; HF: heart failure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Cr: creatinine; Hb: hemoglobin; NT-proBNP: N-terminal portion of B-type natriuretic peptide; ACE inh.: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blocker.

3.3. Factors Related to Mortality

In the univariate analysis (Table 3), female sex, obesity, systolic blood pressure, statin, ACE inhibitors or ARBs, and beta-blockers intake were significantly related to lower mortality. On the other hand, age, presence of dementia, atrial fibrillation, COPD, neoplasia, anemia, hyponatremia, eGFR<60 ml/min, ≤ 60 Barthel index, NYHA functional class III or IV, aldosterone antagonists and digoxin intake were significantly associated with higher mortality.

In multivariate Cox regression analysis, statins were independently associated with lower 1-year mortality, as were female sex, and obesity. In contrast, dementia, anemia, eGFR <60 ml/min, hyponatremia, NYHA classes III-IV, functional impairment (Barthel Index ≤ 60), aldosterone antagonists and digoxin were independent predictors of mortality (Table 3).

Table 3. Univariate and multivariate analysis (Cox Regression) of factors related to overall mortality.

	Overall			
	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	**p**	**HR (95% CI)**	**p**
Age	1.04 (1.03-1.06)	**<0.001**	1.02 (1.01-1.04)	**<0.001**
Women	0.79 (0.65-0.97)	**0.02**	0.72 (0.59-0.87)	**<0.001**
Hypertension	0.97 (0.72-1.31)	0.83	___	
Diabetes	1.05 (0.87-1.23)	0.59	___	
Dyslipidemia	1.11 (0.92-1.35)	0.27	___	
Obesity (BMI>30)	0.70 (0.58-0.86)	**0.001**	0.76 (0.64-0.94)	**0.008**
Myocardial infarction	1.15 (0.89-1.47)	0.28	___	
Atrial fibrillation	1.28 (1.05-1.56)	**0.017**	0.99 (0.82-1.21)	0.945
COPD	0.77 (0.62-9.95)	**0.015**	1.13 (0.92-1.40)	0.246
Dementia	2.17 (1.51-3.15)	**0.009**	1.53 (1.11-2.11)	**0.009**
Neoplasia	1.51 (1.14-1.99)	**0.004**	1.22 (0.95-1.57)	0.129
Anemia	1.59 (1.30-1.94)	**<0.001**	1.28 (1.06-1.55)	**0.011**
eGFR< 60 mL/min/1.73 m²	1.71 (1.40-2.10)	**<0.001**	1.57 (1.30-1.91)	**<0.001**
Hiponatremia	1.48 (1.15-1.89)	**0.002**	1.26 (1.01-1.58)	**0.040**
Barthel Index ≤60	2.36 (1.88-2.95)	**<0.001**	1.77 (1.43-2.18)	**<0.001**
NYHA (III-IV)	1.90 (1.56-2.31)	**<0.001**	1.56 (1.30-1.87)	**<0.001**
SBP	0.99 (0.990-0.997)	**0.001**	0.99 (0.994-1.001)	0.223
HR	0.997 (0.99-1.00)	0.14	___	
ACE inh o ARBs	0.78 (0.64-0.95)	**0.012**	0.93 (0.78-1.12)	0.465
Beta-blockers	0.82 (0.67-0.98)	**0.032**	0.96 (0.81-1.16)	0.695
Aldosterone antagonists	1.30 (1.05-1.61)	**<0.001**	1.34 (1.10-1.62)	**0.004**
Digoxin	1.40 (1.11-1.76)	**0.004**	1.34 (1.08-1.66)	**0.007**
Statins	**0.65 (0.53-0.80)**	**<0.001**	**0.74 (0.61-0.89)**	**0.002**

Legend: OR: Odds ratio; HR: Hazard ratio; 95% CI: 95% confidence Interval. BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; NYHA: Functional Classification of the New York Heart Association; SBP: systolic blood pressure; HR: heart rate; ACE inh.: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blocker.

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When analyzing separately whether statins influenced mortality in patients with or without ischemic heart disease (Table 4), it was observed that, in patients without ischemic heart disease, statin use was independently associated with reduced mortality (OR:0.69; 95% CI:0.56-0.86; p<0.001). However, in patients with HFpEF and ischemic heart disease, there was no association between statin treatment and mortality (OR:0.69; 95% CI:0.43-1.11; p=0.110).

Table 4. Univariate and multivariate analysis of factors related to mortality in patients without and with ischemic heart disease.

	Without ischemic heart disease				**With ischemic heart disease**			
	Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
	OR (CI 95%)	***p***	**HR (CI 95%)**	***p***	**OR (CI 95%)**	***p***	**HR (CI 95%)**	***p***
Age	1.05 (1.03-1.07)	**<0.001**	1.03 (1.02-1.04)	**<0.001**	1.01 (0.98-1.01)	0.500	1.00 (0.97-1.04)	0.861
Women	0.81 (0.66-1.01)	**0.061**	0.76 (0.61-0.94)	**0.012**	0.74 (0.46-1.18)	0.200	0.69 (0.44 – 1.07)	0.098
Hypertension	1.02 (0.74-1.41)	0.910	___		0.69 (0.32-1.48)	0.340	___	
Diabetes	0.96 (0.77-1.18)	0.680	___		0.87 (0.54-1.40)	0.550	___	
Dyslipidemia	0.84 (0.69-1.05)	0.122	___		1.14 (0.70-1.88)	0.620	___	
Obesity (BMI>30)	0.70 (0.56-0.86)	**0.001**	0.77 (0.63-0.95)	**0.013**	0.78 (0.48-1.28)	0.330	___	
Atrial fibrillation	1.38 (1.10-1.72)	**0.006**	1.03 (0.83-1.28)	0.788	0.99 (0.62-1.59)	0.980	___	
COPD	1.29 (1.01-1.63)	**0.038**	1.16 (0.92-1.46)	0.214	1.41 (0.83-2.39)	0.200	___	
Dementia	2.07 (1.38-3.11)	**<0.001**	1.40 (0.98-2.00)	0.069	2.77 (1.16-6.65)	**0.017**	2.17 (1.07-4.41)	**0.032**
Neoplasia	1.42 (1.06-1.95)	**0.019**	1.19 (0.90-1.56)	0.228	1.91 (0.97-3.77)	0.057	___	
Anemia	1.70 (1.36-2.11)	**<0.001**	1.28 (1.04-1.58)	**0.020**	1.09 (0.67-1.79)	0.730	___	
eGFR< 60 mL/min/1.73 m²	1.84 (1.47-2.31)	**<0.001**	1.67 (1.35-2.07)	**<0.001**	1.17 (0.72-1.91)	0.530	___	
Hiponatremia	1.47 (1.11-1.92)	**0.006**	1.23 (0.96-1.57)	0.102	1.54 (0.84-2.79)	0.160	___	
Barthel Index ≤60	2.39 (1.86-3.06)	**<0.001**	1.82 (1.45-2.29)	**<0.001**	2.20 (1.28-3.77)	**0.004**	1.66 (0.99-2.78)	0.054
NYHA (III-IV)	1.97 (1.59-2.44)	**<0.001**	1.52 (1.25-1.87)	**<0.001**	1.58 (0.97-2.57)	0.060	1.45 (0.92-2.23)	0.108
SBP	0.992 (0.988-0.996)	**<0.001**	0.99 (0.993-1.001)	0.165	0.999 (0.991-1.007)	0.780	___	
HR	0.993 (0.988-0.998)	**0.008**	0.99 (0.992-1.001)	0.139	1.015 (1.004-1.026)	**0.007**		
ACE inh o ARBs	0.79 (0.64-0.98)	**0.032**	0.98 (0.80-1.19)	0.811	1.015 (1.004-1.026)	**0.007**		
Beta-blockers	0.86 (0.70-1.06)	0.160	___		0.53 (0.33-0.87)	**0.010**	0.64 (0.41-0.99)	**0.047**
Aldosterone antagonists	1.83 (1.45-2.31)	**<0.001**	1.50 (1.22-1.85)	**<0.001**	0.69 (0.38-1.26)	0.230	___	
Digoxin	1.40 (1.10-1.79)	**0.006**	1.35 (1.08-1.71)	**0.010**	1.53 (0.78-3.04)	0.210	___	
Statins	**0.61 (0.49-0.77)**	**<0.001**	**0.69 (0.56-0.86)**	**<0.001**	0.69 (0.43-1.11)	0.110	___	

Legend: OR: odds ratio; HR: hazard ratio; 95% CI: 95% confidence Interval. BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; NYHA: Functional Classification of the New York Heart Association; SBP: systolic blood pressure; HR: heart rate; ACE inh.: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blocker.

4. Discussion

This study shows that statin therapy is independently associated with lower mortality in patients with HFpEF, primarily in patients without ischemic heart disease.

Patients receiving statins had more vascular risk factors, including hypertension, diabetes, dyslipidemia, and obesity. Similarly, they had more history of established vascular disease such as myocardial infarction, ischemic stroke, and peripheral artery disease. These results are to be expected, given the indication of statins for the treatment of hypercholesterolemia and for primary and secondary prevention of vascular disease [34,35]. Along the same lines is the finding that a higher

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percentage of patients with ischemic HF were treated with statins. Also, these patients received more antihypertensive drugs including ARA II and beta-blockers, and less digoxin, probably because of the lower prevalence of atrial fibrillation in these patients.

In addition, statin-treated patients had better functional and mental status, with less dementia, despite the higher prevalence of cardiovascular disease. Although the better situation could be at least partially attributed to the younger age of the statin-treated patients, the age difference between the two groups was very small (less than one year), so it probably had little influence on this aspect. Conversely, the better functional and mental status of the patients receiving statins, with a longer life expectancy, may have influenced the higher prescription of these drugs. These patients also had better NYHA functional class.

The independent association between statins and lower mortality in HF patients has been previously described in several studies, most of them observational [9–26,36]. The *GISSI* study was the only clinical trial conducted that included patients with HFrEF and HFpEF [28], analyzing each group separately. It did not show a significant decrease in mortality. However, the low percentage of patients with HFpEF in the study (10%) may have precluded assessment of the effect of statins in this subgroup. In addition, patients with mildly reduced LVEF were included in the HFpEF group (HFpEF was defined as those with LVEF greater than 40%), who have been shown to have more similar characteristics to HFrEF [3]. A minority of studies have shown no reduction in mortality [10,22,23]. However, there have been several meta-analyses [9,20,26,27], one of them published recently [26], showing the benefit of statin use, given its association with a reduction in total mortality in patients with HFpEF.

Most previous studies have assessed the reduction in overall mortality and some of them also assessed cardiovascular mortality. Notably, it has been suggested that the mortality benefit is mainly due to a reduction in sudden death and non-cardiovascular death [10]. In addition, mortality reduction has been reported in patients without ischemic heart disease [12,15,25]. Specifically, a subanalysis of the TOPCAT clinical trial found a reduction in all-cause and cardiovascular mortality in patients without ischemic heart disease, an effect that was not observed in patients with ischemic heart disease [15]. These results are consistent with those observed in our study. Furthermore, another recent observational study showed that statins reduced mortality and cardiovascular events separately. An interesting aspect of this study is that it had a large sample of patients and those with cardiovascular disease were excluded. Thus, statins were assessed only as primary prevention [37].

The pathophysiology of HFpEF is complex and different from HFrEF [38,39]. Treatments such as ACE inhibitors, ARBs, beta-blockers, and aldosterone antagonists are part of the optimal therapy in patients with HFrEF, because of their benefit in reducing mortality, which has not been achieved in patients with HFpEF [22]. This supports the premise that they are differentiated groups of patients and contributes to the understanding that a pharmacological group may be useful for one type of HF, but not for the other, as may be the case with statins [28,40]. These drugs, in addition to their widely known action on LDL-cholesterol levels, are postulated to have numerous effects related to the development and progression of HFpEF [41]. These include beneficial effects on ventricular remodeling, with reduced left ventricular hypertrophy and fibrosis and prevention of left ventricular dilatation in both animal models and patients. A mild antihypertensive effect is added in hypertensive patients [42], as well as an improvement in arterial distensibility, due to improved endothelial function and reduced atherosclerosis, with plaque stabilization [43]. Thus, reducing afterload and improving coronary perfusion. These results imply an improvement in left ventricular relaxation and diastolic function [44].

These effects are also associated with a decrease in the frequency of atrial fibrillation development [45]. Indeed, in our study, a lower prevalence of atrial fibrillation was observed in patients treated with statins. It is also thought to reduce ventricular tachyarrhythmias, both through its "anti-remodeling" effect and its effects on microcirculation and ischemia, as well as by normalizing sympathetic innervation, which may benefit those with excess catecholaminergic activity. In particular, it has been associated with reduced QT interval variability, QT shortening and increased pulse variability [46]. This may be implicated in the reduction of sudden death in these patients [18].

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In addition, it is believed that its benefits may be related to its anti-inflammatory and antioxidant capacity, causing a decrease in analytical parameters such as C-reactive protein (CRP) or brain natriuretic peptide (BNP), which is advantageous considering the involvement of systemic inflammation in the pathophysiology of HFpEF [26,38]. Some authors consider that many patients with HFpEF have subclinical ischemia and even if they do not have macrovascular ischemic disease demonstrated by events or angiography, statins have a benefit at that level [19,40].

Indeed, as mentioned at the outset, our study shows that the mortality benefit of statins occurs in patients without ischemic heart disease, which supports that it is not only due to their lipid-lowering effect. Other studies also support this position [9,15,24,25].

It should be noted that the decrease in mortality of statins in these patients could be associated with their benefits in other comorbidities (renal failure, diabetes, infections) [10,34], in addition to pure vascular effects mentioned above.

In addition to statins, other factors independently related to lower mortality were female sex and obesity. While worse NYHA functional status, the presence of renal disease, anemia, hyponatremia and dementia were independently associated with higher mortality. This could be expected given that, these are poor prognostic factors widely described in the literature [2,39].

Interestingly, aldosterone antagonists were associated with an increase in mortality in multivariate analysis. Other studies demonstrate their lack of effectiveness on survival in HFpEF, as previously mentioned [22]. That they are also associated with increased mortality may be due to their use in patients who are more refractory to treatment, with more comorbidities, or to the adverse effects of the medication. Digoxin was also associated with increased mortality, probably due to its association with the diagnosis of atrial fibrillation and the comorbidity that this entails in patients with HFpEF.

On the other hand, statin-treated patients had more readmissions overall and for HF. Reduced readmissions with statin use have been reported in the literature [11,40], although not unanimously [10]. The higher number of admissions of these patients could be related to the decrease in mortality.

Several observational studies claim that some of these effects are ineffective after established cardiac hypertrophy or dilatation or high NYHA functional class. Specifically the "anti-remodeling" effect and symptom-reducing effect [10,24]. These findings may indicate the importance of early treatment of patients with incipient or non-advanced HFpEF to prevent, delay or reduce the deleterious effects related to cardiac remodeling. This may imply considering the possibility of a lower success rate in patients with advanced heart disease, with the consequent likelihood of a higher number of treatment-related adverse effects.

On the other hand, some studies have found that low cholesterol levels are associated with increased mortality [47]. This could be related to the advanced stage of HF and consequent secondary malnutrition, in the same sense that lower BMI is associated with increased mortality, a phenomenon known as the "obesity paradox" [48]. Such a result is observed in our study, as patients with obesity have lower mortality after adjusting for other risk factors.

The study has several limitations. First, it is an observational study, which does not allow us to attribute causality. In addition, residual confounding factors may exist. However, a large sample of patients was collected from multiple hospitals nationwide.

Secondly, cholesterol levels were not collected, making it difficult to assess whether the effect of statins is independent of cholesterol reduction.

Thirdly, neither the type of statins (low or high intensity, lipophilic or hydrophilic), nor the dose, duration of treatment was collected. Therefore, despite evidence of a greater effect of lipophilic and high-intensity statins [9,24,26], we were unable to analyze these data. However, most studies do not have these data available either [27].

As previous studies indicate, clinical trials are needed to definitively establish the association between statin use and lower mortality in patients with HFpEF. This is particularly relevant in this pathology where only one pharmacological group has been shown to reduce mortality. Although the available evidence comes from observational studies, several meta-analyses highlight the potential benefit of reducing mortality [9,20,26,27]. Therefore, a mention on the potential benefit of statin use

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in patients with HFpEF should be considered for inclusion in HF clinical practice guidelines, and at least explicit mention should be made of the main studies and meta-analyses showing these results.

5. Conclusions

Statin use is independently associated with lower 1-year mortality in patients with HFpEF, particularly those without ischemic heart disease. However, it does not correlate with reduced rates of total or heart failure-specific readmissions. These findings, supported by various meta-analyses, suggest that guidelines for HFpEF treatment should potentially include a mention of statins' beneficial effects.

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Institutional review board statement: The RICA registry protocol conforms to the ethical guidelines of the Declaration of Helsinki and it was approved by the Ethics Committee of the Hospital Universitario Reina Sofía (Córdoba) (protocol code 18/349-E, last updated on 9 August 2018, approval date 23 October, 2007) and all patients signed the informed consent before being included in the RICA cohort.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Appendix A. RICA Registry Members

Álvarez Rocha P, Anarte L, Aramburu-Bodas O, Arévalo-Lorido JC, Cabanes Hernández Y, Carrascosa S, Carrera Izquierdo M, Casado Cerrada J, Conde-Martel A, Chivite D, Díez-Manglano J, Epelde F, Formiga F, García Escrivá D, Gómez del Olmo V, González Franco A, Llacer P, López-Castellanos, G, Manzano L, Martín Ezquerro A, Montero-Pérez-Barquero M, Moreno García MC, Muela A, Ormaechea G, Pérez Calvo JI, Pérez-Silvestre J, Quirós López R, Romero M, Ruíz Ortega R, Satué Bartolomé JA, Soler-Rangel L, Suárez-Pedreira I, Trullàs JC.

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